

What is claimed is:

1. A method for making a drug-containing particulate product, comprising:
contacting a drug-containing feed solution with a compressed anti-solvent fluid to precipitate drug-containing particles, the feed solution including the drug in a cosolvent system including at least a first organic solvent and a second organic solvent that are mutually soluble; and
separating the drug-containing particles from the anti-solvent fluid.
2. The method of Claim 1, wherein drug is at least an order of magnitude more soluble in the first organic solvent than in the second organic solvent.
- 10 3. The method of Claim 1, wherein the first organic solvent and the second organic solvent are present in the solution at a volume ratio of the second organic solvent to the first organic solvent of larger than 30:70.
4. The method of Claim 1, wherein the first organic solvent and the second organic solvent are present in the cosolvent system at a volume ratio of the second organic solvent to the first organic solvent of from 50:50 to 90:10.
- 15 5. The method of Claim 1, wherein the first organic solvent is selected from the group consisting of DMSO and DMFA.
6. The method of Claim 5, wherein the second organic solvent is an alcohol.
7. The method of Claim 5, wherein the second organic solvent is a C1-C5
20 alkanol.
8. The method of Claim 1, wherein the compressed anti-solvent, during the contacting, is at a reduced pressure of larger than 0.8 and a reduced temperature of larger than 0.95.
9. The method of Claim 8, wherein the compressed anti-solvent, during the
25 contacting, is at a reduced pressure of larger than 0.9.
10. The method of Claim 8, wherein the compressed anti-solvent, during the contacting, is in a supercritical state.
11. The method of Claim 8, wherein the compressed anti-solvent comprises compressed carbon dioxide.
- 30 12. The method of Claim 1, wherein the compressed anti-solvent fluid consists essentially of only compressed carbon dioxide.

13. The method of Claim 1, wherein the feed solution is substantially free of amphiphilic materials that improve solubility of the drug in the feed solution through hydrophobic ion pairing with the drug.

14. The method of Claim 1, wherein, during the contacting step, the solution 5 is introduced into a flow of the compressed anti-solvent fluid with a direction of flow of the solution being at an angle of from 45° to 180° relative to the direction of flow of the compressed anti-solvent fluid.

15. The method of Claim 1, wherein the cosolvent system includes water, if at all, in an amount of smaller than 5 weight percent.

10 16. The method of Claim 1, wherein the cosolvent system is substantially free of water.

17. The method of Claim 1, where at least a portion of the drug in the feed solution is in the form of colloidal particles dispersed in the cosolvent system.

18. The method of Claim 1, wherein the drug is selected from the group 15 consisting of a protein, a peptide and a genetic material.

19. The method of Claim 1, wherein the drug is a protein.

20. The method of Claim 1, wherein the drug is insulin.

21. The method of Claim 1, wherein the concentration of the drug in the feed solution system is smaller than 0.3 mg of the drug per milliliter of the feed solution.

20 22. The method of Claim 1, wherein, during the contacting step, the solution is introduced into the compressed anti-solvent fluid through an opening having a cross-sectional area available for flow of larger than 1 square millimeter.

23. The method of Claim 1, wherein the contacting step is conducted under 25 conditions so that the particles have a tap density of larger than 0.1 gram per cubic centimeter.

24. The method of Claim 1, wherein the first organic solvent comprises DMSO and the second organic solvent comprises at least one of chloroform, methanol, ethanol and isopropanol.

25. The method of Claim 1, wherein the feed solution comprises 30 dipalmitoylphosphatidylcholine and the particles comprise at least a portion of the dipalmitoylphosphatidylcholine.

26. The method of Claim 1, wherein the feed solution comprises a biocompatible polymer and the particles are multi-component particles comprising at least a portion of the biocompatible polymer.

27. The method of Claim 26, wherein the drug is more soluble in the first 5 organic solvent than is the biocompatible polymer, and the biocompatible polymer is more soluble in the second organic solvent than the drug.

28. The method of Claim 26, wherein the biocompatible polymer is hydrophobic, the first organic solvent being a polar solvent for the drug and the second organic solvent being a nonpolar solvent for the biocompatible polymer.

10 29. The method of Claim 26, wherein the first organic solvent is substantially miscible with water and the second organic solvent is substantially immiscible with water.

15 30. The method of Claim 26, wherein the second organic solvent comprises at least one of methylene chloride, formaldehyde, dioxolane, chloroform, benzene, ethyl ether, toluene, xylene, 1,3-dioxane and THF.

31. The method of Claim 30, wherein the first organic solvent comprises an alcohol.

32. The method of Claim 31, wherein the first organic solvent comprises a C₁-C₅ alkanol.

20 33. The method of Claim 32, wherein the second organic solvent comprises methylene chloride.

25 34. The method of Claim 26, wherein the method comprises, prior to the contacting step, preparing the feed solution, comprising mixing a first solution having the drug dissolved therein with a second solution having the biocompatible polymer dissolved therein, the first solution including the first organic solvent and the second solution including the second organic solvent.

35. The method of Claim 34, wherein during the mixing step, the second solution is added to the first solution.

30 36. The method of Claim 26, wherein the weight ratio of the drug to the biocompatible polymer in the feed solution is larger than 5:95.

37. The method of Claim 26, wherein the weight ratio of the drug to the polymer in the feed solution is in a range of from 5:95 to 50:50.

38. The method of Claim 26, wherein the contacting step is conducted under conditions so that the multi-component particles have a degree of encapsulation of the 5 drug by the polymer of greater than 50 percent.

39. The method of Claim 26, wherein the contacting step is conducted under conditions so that the multi-component particles have a degree of encapsulation of the drug by the polymer of greater than 70 percent.

40. The method of Claim 26, wherein the biocompatible polymer comprises 10 repeating units from polymerization of at least one monomer selected from the group consisting of an alphahydroxycarboxylic acid, a cyclic diester of an alphahydroxycarboxylic acid, a dioxanone, a lactone, a cyclic carbonate, a cyclic oxalate, an epoxide, and a glycol.

41. The method of Claim 26, wherein the biocompatible polymer is selected 15 from the group consisting of poloxamers, polyanhydrides, phosphatriazenes and combinations thereof.

42. The method of Claim 26, wherein the biocompatible polymer comprises a poly(lactic acid).

43. The method of Claim 26, wherein the drug is selected from the group 20 consisting of a peptide, a protein and genetic material.

44. The method of Claim 26, wherein the drug is insulin.

45. A particulate product including particles made according to the process of Claim 1.

46. A particulate product for pulmonary delivery of a drug, comprising: 25 a powder batch of particles including at least one drug, the powder batch having a tap density of from 0.1 to 0.5 grams per cubic centimeter and being aerosizable by an inhaler to produce an aerosol having dispersed particles comprising the drug and being suspended in a carrier gas, the dispersed particles having a mass median aerodynamic diameter of smaller than about 6 microns.

30 47. The particulate product of Claim 46, wherein the mass median aerodynamic diameter is smaller than about 5 microns.

48. The particulate product of Claim 46, wherein the mass median aerodynamic diameter is smaller than about 4 microns.

49. The particulate product of Claim 46, wherein at least some of the particles of the powder batch are large particle units having an envelope diameter of at least 10 microns, the powder batch being aerosizable in the inhaler to break apart at least a portion of the large particle units to produce at least a portion of the dispersed particles in the aerosol.

50. The particulate product of Claim 49, wherein the large particle units have an envelope diameter of larger than about 25 microns.

10 51. The particulate product of Claim 49, wherein the large particle units have an envelope diameter of larger than about 50 microns.

52. The particulate product of Claim 49, wherein the large particle units are substantially not spherical in shape.

15 53. The particulate product of Claim 46, wherein the drug comprises a member selected from the group consisting of peptides, proteins and genetic material.

54. The particulate product of Claim 46, wherein the drug comprises insulin.

55. The particulate product of Claim 46, wherein the powder batch is contained within a receptacle receivable by the inhaler, the receptacle being adapted to operate with the inhaler so, that when the receptacle is received by the inhaler, the inhaler 20 is actuatable to aerosolize the powder batch from the receptacle to produce the aerosol.

56. The particulate product of Claim 55, wherein the powder batch is sized to include only a unit dose of the drug.

25 57. The particulate product of Claim 56, wherein the receptacle comprises a plurality of containers each containing a different one of said powder batch, the inhaler being successively actuatable to successively aerosolize each said powder batch.

58. The particulate product of Claim 55, wherein the powder batch is in the form of a substantially dry powder.

30 59. The particulate product of Claim 46, wherein the particles of the powder batch are dispersed in a propellant fluid and contained within the inhaler, the inhaler being actuatable to permit the propellant fluid to expand to produce a single dose aerosol.

60. A method for generating an aerosol for pulmonary delivery of drug comprising aerosolization of the particulate product of Claim 46 to produce the aerosol of Claim 46.

61. An apparatus for generating a drug-containing aerosol for pulmonary delivery of a drug, comprising:

an inhaler having disposed therein the particulate product of Claim 46, the inhaler being actuatable to aerosolize the powder batch to produce the aerosol of Claim 46.

62. The inhaler of Claim 61, wherein the powder batch is in the form of a substantially dry powder.

63. The inhaler of Claim 61, wherein the inhaler is a dry powder inhaler.

64. A particulate product comprising a multi-component material including a drug and a biocompatible polymer and having a degree of drug encapsulation of larger than 30 percent, the particulate product being aerosolizable by an inhaler to produce an aerosol including dispersed particles of the multi-component material, said dispersed particles having a mass median aerodynamic diameter of smaller than 6 microns.

65. The particulate product of Claim 64, wherein the degree of drug encapsulation is larger than 50 percent.

66. The particulate product of Claim 64, wherein the degree of drug encapsulation is larger than 70 percent.

67. The particulate product of Claim 64, wherein the degree of drug encapsulation is larger than 80 percent.

68. The particulate product of Claim 64, wherein the mass median aerodynamic diameter is smaller than 6 microns.

69. The particulate product of Claim 64, wherein the mass median aerodynamic diameter is in a range of 0.5 to 4 microns.

70. The particulate product of Claim 64, wherein the mass median aerodynamic is in a range of 0.5 to 3 microns.

71. The particulate product of Claim 64, wherein the particulate product comprises large particle units having an envelope diameter of larger than 10 microns.

72. The particulate product of Claim 71, wherein the envelope is larger than 25 microns.

73. The particulate product of Claim 71, wherein the envelope diameter is larger than 50 microns.

74. The particulate product of Claim 71, wherein the large particle units are each comprised of primary particles having a mass median diameter of smaller than about 5 microns.

75. The particulate product of Claim 71, wherein the particulate product is aerosizable by the inhaler to break apart at least a portion of the large particle units to form at least a portion of the dispersed particles in the aerosol.

76. The particulate product of Claim 64, wherein the multi-component particles include a weight ratio of the drug to the biocompatible polymer of larger than 5:95.

77. The particulate product of Claim 64, wherein the multi-component particles include a weight ratio of the drug to the biocompatible polymer in a range of from 5:95 to 50:50.

78. The particulate product of Claim 64, wherein the drug is selected from the group consisting of a peptide, a protein and genetic material.

79. The particulate product of Claim 64, wherein the drug is insulin.

80. The particulate product of Claim 64, wherein the particulate product comprises at least one powder batch contained within an inhaler actuatable to aerosolize the powder batch to produce the aerosol.

81. The particulate product of Claim 64, wherein the particulate product comprises at least one powder batch contained within a receptacle receivable by the inhaler, the receptacle being adapted to operate with the inhaler so that, when the receptacle is received by the inhaler, the inhaler is actuatable to aerosolize the powder batch from the receptacle to produce the aerosol, the powder batch being sized for a unit dose of the drug.

82. The particulate product of Claim 81, wherein the receptacle comprises a plurality of containers each containing one said powder batch, the receptacle being adapted to operate with the inhaler so that when the receptacle is received by the inhaler, the inhaler is successively actuatable to aerosolize the powder batch from different ones of the compartments.

83. The particulate product of Claim 81, wherein the multi-component material is in the form of a substantially dry powder.

84. The particulate product of Claim 64, wherein the multi-component material is in the form of a substantially dry powder contained within the inhaler 5 actuatable to aerosolize the powder batch to produce the aerosol.

85. The particulate product of Claim 64, wherein the multi-component material is in the form of particles dispersed in a propellant fluid and contained within the inhaler, the inhaler being actuatable to permit at least a portion of the propellant fluid to expand to produce a single dose aerosol.

10 86. The particulate product of Claim 64, wherein the multi-component particles have a tap density of larger than about 0.1 grams per cubic centimeter.

87. The particulate product of Claim 64, wherein the biocompatible polymer comprises repeating units from polymerization of at least one monomer selected from the group consisting of an alphahydroxycarboxylic acid, a cyclic diester of an 15 alphahydroxycarboxylic acid, a dioxanone, a lactone, a cyclic carbonate, a cyclic oxalate, an epoxide, and a glycol. Preferred biocompatible polymers comprise at least some repeating units representative of polymerizing at least one of lactic acid, glycolic acid, lactide, glycolide, ethylene oxide, ethylene glycol and combinations thereof.

88. The particulate product of Claim 64, wherein the biocompatible polymer 20 is selected from the group consisting of poloxamers, polyanhdydrides, phosphatriazenes and combinations thereof.

89. The particulate product of Claim 64, wherein the biocompatible polymer comprises poly(lactic acid).

90. A method for generating an aerosol for pulmonary delivery of a drug 25 comprising aerosolization of the particulate product of Claim 64 to produce the aerosol of Claim 64.

91. An apparatus for generating a drug-containing aerosol for pulmonary delivery of a drug, comprising:

30 an inhaler having disposed therein the particulate product of Claim 64, the inhaler being actuatable to aerosolize the particulate product of Claim 64 to produce the aerosol of Claim 64.

92. The inhaler of Claim 91, wherein the powder batch is in the form of a substantially dry powder.

93. The inhaler of Claim 91, wherein the inhaler is a dry powder inhaler.